REMARKS

Applicant wishes to thank the Examiner for the careful consideration given this case. Claims 1, 3, 10-16, 21, and 22 are pending in this case, with Claims 2, 4-9, 17-20, and 23-27 being hereby cancelled without prejudice to their pursuit in this or related cases. All claim amendments are fully supported by the specification and satisfy the statutory requirements of enablement and written description. Applicant requests that the Examiner consider the remarks and amendments presented herein. This response addresses those issues raised in the Office Action mailed on August 27, 2003. It is submitted that, as they currently stand, the claims are in condition for allowance. Communication to this effect is respectfully requested.

Claim objections

The Examiner objects to Claims 1, 14, and 21-22 for grammatical and incorrect dependency errors. These claims have been amended to address the concerns of the Examiner. Reconsideration is respectfully requested.

Written description rejection under §112, ¶1

The Examiner rejects Claims 1, 3, 10-16, and 21-22 under 35 U.S.C. § 112, first paragraph as lacking a clear written description of "a portion for binding to a specific target cell." The Examiner notes that the pending claims are drawn to a compound (a protein) comprising a portion for binding to a specific target cell and a cytotoxic portion, which is a constitutively active caspase. The Examiner asserts that no common structure attributes that identify the claimed "portion for binding to a specific target cell" are disclosed and further that no common functional attributes that identify that portion are disclosed. The Examiner, citing *The*

Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) and the Interim Written Description Guidelines, concludes that the disclosure does not support the claimed genus and fails the written description requirement. The Examiner finally notes that a compound comprising an antibody specific for a target cell and a cytotoxic portion (which is a constitutively active caspase or has the same apoptosis-inducing activity as said caspase), wherein the cytotoxic portion is conjugated to said antibody, satisfies the written description provision.

Initially, Applicant would like to thank the Examiner for the indication that the subject matter of a compound comprising an antibody specific for a target cell and a cytotoxic portion (which is a constitutively active caspase or a protein has the same apoptosis-inducing activity as said caspase), wherein the cytotoxic portion is conjugated to said antibody, satisfies the written description provision. Nevertheless, Applicant disagrees with the Examiner's application of *Lilly* and conclusions regarding the satisfaction of the written description requirement of § 112 by the presently-pending claims.

As is consistently stated throughout the present specification, the present invention relates to compounds that are general tools for delivering a constitutively active caspase or a protein that has the same apoptosis-inducing activity as said caspase to a target cell. The currently-claimed invention recites the well known class of molecules that allow for binding to a specific target cell. Certainly, antibodies are a commonly known example of molecules that allow for targeting of a specific cell type. However, by no means are antibodies the only well known molecules that are capable of such specific targeting. Further and in contrast to the characterizations of the Examiner, non-antigenic molecules <u>are</u> clearly described in the present specification. The specification discloses on page 22,

lines 12-21 that the target to be bound could be a non-antigenic molecule, and as such the portion for binding to a specific cell would bind in a non-immune sense, *e.g.* as a substrate or analog thereof. The specific examples of melaoncyte-stimulating hormones (MSH) and vascular endothelial growth factor (VEGH) receptors accompany this broad disclosure.

It is accepted law that even a single example coupled with a broad disclosure supports the claiming of a genus. In *In re Herschler* (591 F.2d 693 CCPA, 1979), the Court found that a disclosure of a corticosteroid in DMSO was sufficient to support generic claims drawn to a method of using a mixture of "a physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description." *Herschler* 591 F.2d 693, 697. *See also* Footnote 55 in the "Guidelines for the Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement" Fed. Reg., Vol. 66(4), 2001, 1099-1111. It is respectfully submitted that the present case is just such a circumstance as is described in *Herschler*. One of skill in the art would be led to the class of compounds that satisfy the limitation "portion for binding to a specific target cell" by the functional recitation of that class of compounds in the present specification. According to the test of *Herschler* and the final Written Description Guidelines, the present claims unequivocally satisfy the written description requirement of § 112, ¶1.

The claimed molecules of the present invention that include "a portion for binding to a specific target cell" would be clearly recognized and understood by

one of skill in the art to be invented by and possessed by the Applicant. Given that numerous examples of molecules having such properties are disclosed in the present specification and that the specification further broadly discloses the claimed genera, it clearly describes to the skilled practitioner a genus of molecules that includes both antigenic and non-antigenic cell targeting molecules.

While the Examiner asserts that *Lilly* controls the present situation, the Applicant respectfully submits that the Federal Circuit has clarified its position on *Lilly* in *Amgen v. Hoechst Marion Roussel* (314 F.3d 1313, CAFC 2003) and that this decision is more germane to the presently-pending claims. In this decision, the Court evaluated whether a claim that recited the genus of vertebrate and mammalian cells was sufficiently supported by the specification. As the Court noted at *Amgen* 1332:

> Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend...This difference alone sufficiently distinguishes *Eli Lilly*, because when used, as here, merely to identify types of cells (instead of undescribed, **previously unknown** DNA sequences), the words "vertebrate" and "mammalian" readily "convey[ ] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." (quoting *Lilly*, emphasis added)

It is respectfully submitted that the claimed element of "portion for binding to a specific target cell" is not a new or unknown biological material that ordinarily skilled artisans would easily miscomprehend. Instead, the claimed element of "portion for binding to a specific target cell" recites a known class of molecules that one of skill in the art would easily recognize and that the phrase conveys distinguishing information concerning their identity. There is no doubt that a skilled artisan would visualize or recognize the identity of the members of

this genus. Accordingly, the *Lilly* written description standard, as interpreted and refined in *Amgen*, is unequivocally and clearly satisfied. Reconsideration and withdrawal of this rejection is respectfully requested.

Enablement rejection under 35 U.S.C. § 112, ¶1

The Examiner further rejects Claims 1, 3, 10-16, and 21-22 under 35 U.S.C. § 112, first paragraph pertaining to lack of enablement for a compound comprising "a portion for binding to a specific target cell" and a cytotoxic portion. The Examiner argues that the claims encompass any compound that binds to a specific target cell, wherein one cannot predict whether said compound would be internalized and whether the claimed conjugate would be delivered to proper cellular compartment where the caspase exerts its action. The Examiner further states that the specification only discloses antibodies or fragments thereof that bind to various antigens or receptors on pages 14-23 and a conjugate of an antibody fragment scFv against CEA and a rearranged, constitutively active caspase on pages 58-58 and in Figure 9.

Applicant strongly disagrees with the Examiner characterization of the specification. Applicant discloses numerous examples of antigenic targeting molecules on pages 14-23 and also disclose non-antigenic targeting molecules on page 22, lines 12-21, both generically and with specific examples. It is unclear to the Applicant how, in light of these numerous examples, could suggest that the "specification only discloses a single example of a target cell specific portion, antibodies or fragments thereof that bind to various antigens or receptors." The claims are clearly enabled on this point. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner also rejects Claims 1, 3, 10-16, and 21-22 under 35 U.S.C. § 112, ¶1 pertaining to lack of enablement for a compound comprising a portion for binding to a specific target cell and a cytotoxic portion, which is "any constitutively active caspase, or has the same apoptosis-inducing activity as said caspase." The Examiner discusses procaspase-3 as a poor inducer of cell death and suggests that it is unpredictable that a compound comprising a portion for binding to a specific target cell and a cytotoxic portion, which has the same apoptosis-inducing activity as a constitutively active caspase, *i.e.* *any caspase*, would be useful for anything (page 6, last paragraph of the present Office Action). The Examiner appears to believe that the phrase "constitutively active" includes any caspase once activated. However, the phrase "constitutively active caspase" describes a caspase that is active without interacting with any other factors or molecules.

The Examiner cites Colussi *et al.* as describing autocatalytic caspases. The caspases discussed by Colussi *et al.* are only able to autocatalyze **after** oligomerization of more than one caspase molecule. The autocatalytic caspases of Colussi *et al.* are distinct from the caspases of the present invention, which instead are inherently active after translation or able to autocatalyze without interaction with other factors. Srinivasula *et al.* supports Applicant's position because therein it describes autocatalytic and constitutively active caspases as distinct types of caspases. Srinivasula *et al.* discuss the need for autocatalytic caspases to interact with a complex of other caspase molecules (page 10107, right column, second paragraph). In contrast, the constitutively active caspases are described as autocatalytic in the absence of other factors (page 10108, left column, second paragraph).

The difference between mere autocatalysis and constitutive activity is defined clearly in the art, *e.g.* Srinivasula *et al.* Therefore, the use of the phrase "constitutively active caspase" in the present claims is well defined and perfectly clear to one of skill in the art.

Additionally, the Examiner has argued that activated caspases would be inhibited by caspase inhibitors before reaching their target cell. The Examiner cites the existence of blood borne serine protease inhibitors as support for this contention. However, the specification discloses at Example H that a caspase conjugate compound possessing a constitutively active caspase is effective in producing an apoptotic effect. Example H provides an experimental situation wherein cells are incubated in serum. The inhibitory molecules that the Examiner discusses would be present in the serum in the culture medium. Clearly, Example H shows that caspase is effective in inducing apoptosis and therefore the Examiner's hypothesis regarding inhibitory molecules may be rejected. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner rejects Claims 1, 3, 10-16, and 21-22 under 35 U.S.C. § 112, ¶1 pertaining to lack of enablement for a compound comprising a portion for binding to a specific target cell and a cytotoxic portion, which is a constitutively active caspase "or has the same apoptosis-inducing activity as said caspase." Applicant has amended the pending claims herein to remove this phrase, thus rendering this rejection moot. Reconsideration and withdrawal of the present rejection is respectfully requested.

The Examiner rejects Claims 21-22 under 35 U.S.C. § 112, ¶1 pertaining to a lack of enablement for a pharmaceutical composition or a compound for use in medicine. The Examiner's argument, in large part, is based on the

objection that *in vitro* data do not provide sufficient support for all of the functions that an immunoconjugate must fulfill *in vivo*. The Examiner has stated that an immunoconjugate must be "delivered to the circulation supplying the tumor." The compounds of the invention could be administered in a variety of ways. In particular, intravenous administration would introduce the compounds directly into the circulation. Even if a proportion of the conjugates are cleared by the liver and kidney, it is inevitable that the remaining conjugate molecules will remain in the circulation and reach the target tumor. Therefore, the conjugate molecules will reach the target cells.

The Examiner also states that the conjugate molecules must interact with the target site. Clearly, by the nature of the conjugate including a portion that is specific for a target cell, the conjugate molecule will bind to the target cells of interest.

The Examiner states that sufficient concentration must reach the target cells in order to produce an effect. Where the conjugate molecule is administered to a patient, it would be administered in a sufficient amount in order to produce an effect. It is a matter of a medical practioner's day-to-day practice to determine the most appropriate amount of any particular drug to give to a patient in order to produce a desirable clinical effect. Furthermore, Examples C and D of the present specification provide suggested dosing regimes for the conjugate molecules. Therefore, the compounds of the invention would be administered to a patient at an adequate concentration to produce an effect.

The Examiner has sated that the conjugate must be in contact with the tumor for sufficient time to produce an effect. When the conjugate molecule is administered to patients, it will be provided by administration of repeated doses.

The specification describes administering doses to humans in 3 to 5 day intervals (*see* Examples C and D). Therefore, as the concentration of one dose decreases at the tumor site, the next dose will have been administered and will replace the original conjugates. Repeated dosing will mean that the target cells will be constantly exposed to the conjugates. Therefore, the target cells will be exposed to the conjugates for sufficient time for the conjugates to act.

The Examiner has stated that the cell must not have an alternate means of survival. The Examiner had earlier discussed the presence of inhibitors of caspases *in vivo* that would prevent the active caspases from acting. The arguments presented above, namely that the present invention as disclosed describes the action of caspases in serum-containing culture medium, are relevant on this point.

The Examiner has stated that Schimmer teaches that inhibitory molecules may be over-expressed in cancer cells. However, it is also well known that many genes are underexpressed in some cancer cells, *e.g.* DNA repair enzymes. Therefore, a skilled artisan would also reasonably predict that such inhibitory molecules might also be under-expressed, exacerbating the effectiveness of the conjugates of the invention.

In summary, the administration of chemotherapeutics and treatment of cancer is a well-established and predictable art. The determination of specific regimen conditions and reagent concentrations would not require undue experimentation on the part of the skilled practitioner. Reconsideration and withdrawal of the present enablement rejection is respectfully requested.

The Examiner rejects Claim 14 under 35 U.S.C. § 112, ¶1 pertaining to lack of enablement for a "constitutively active variant" of a naturally occurring caspase having apoptosis-inducing activity. Applicant submits that the specification teaches that variants include deletions, substitutions, and additions, specifically at Page 11, lines 1-9. Furthermore, on page 11, lines 11-12 it is disclosed that variants can be made of any of many common place and routine methods in the art. The skilled practitioner would absolutely be familiar with these practices and it would not require undue experimentation to create such variants.

The Examiner also notes that there is unpredictability in protein chemistry and that this means that the variants may not have biological activity of a caspase. However, the claims are limited so that the variant must possess the same constitutive activity as the wildtype caspases of the invention. This feature limits the variants encompassed by the pending claims to only those which possess caspase activity. Therefore, the Examiner's arguments are not relevant to the claimed caspase variants. Reconsideration and withdrawal of the pending rejection are earnestly solicited.

Obviousness rejection

The Examiner has rejected the claims as being obvious in light of Srinivasula *et al.* (1998) in view of U.S. Patent No. 4,753,894 (the '894 patent); Colussi *et al.* (1998) and Keppler-Hafkemeyer *et al.* (1998). Applicant strongly maintains that Srinivasula *et al.* teach that caspases should be used in gene therapy methods and not the protein-based methods of the present invention. This is supported by the last paragraph of Srinivasula *et al.* whereby possible therapeutic applications are discussed without so much as hinting that a protein-based approach is plausible, let alone possible.

A skilled person would not seek to apply the suggestions of Srinivasula *et al.* by implementing something completely different. The Examiner is using impermissible hindsight to modify Sirinivasula *et al.* in an attempt to reject the present claims. Indeed, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is **some teaching, suggestion, or motivation** to do so either implicitly or explicitly in the references themselves or in the knowledge generally available to one of skill in the art. MPEP § 2143.01. It is respectfully submitted that the Examiner has not established such a teaching, suggestion, or motivation. Indeed, Srinivasula *et al.* do not at all discuss the actual subject matter of the pending claims. Accordingly, the obviousness rejection presented herein are untenable on this point alone. Reconsideration and withdrawal of the present rejection is respectfully requested.

Further, the Examiner contends that Srinivasula *et al.* teach that only low concentrations of caspase 3 and 6 require administration in order to cause apoptosis. However, administration of these caspases in a pharmaceutical setting, as noted above, is intended to be approached via gene therapy. Clearly, a skilled person would know from nature, wherein only one caspase gene activated by normal mechanisms is required to kill a cell, that only low concentrations of targeted gene would be required in order to produce many copies of caspase proteins. This point further illustrates that Srinivasula *et al.* is dealing with different subject matter than the present invention. In fact, Srinivasula *et al.* is arguably not even analogous art in that it deals with gene therapy applications rather than protein-based applications. Its use in the present obviousness rejections by the Examiner is entirely inappropriate. Reconsideration and withdrawal of the pending rejection is earnestly solicited.

The Examiner has also stated that it would be obvious to use the caspases of Srinivasula *et al.* because they are the most downstream executioners of apoptosis and are thus least likely to be inhibited by the apoptosis inhibitors described by Colussi *et al.* While it is true to say that there are fewer cascade steps between the caspase and cell death the further downstream the caspase is, it is also the case that due to amplification and auto-activation of caspases during a cascade, progressively more inhibitory molecules would be required to cause cell death at progressive downstream steps. There is no data to show that any step is better to inhibit than any other. Therefore, the risk of inhibition at any stage of the apoptosis cascade is likely to be very similar.

In fact, it is irrelevant wherein the cascade the inhibition occurs, as the result is the same. If an upstream caspase is inhibited then the cascade would stop, similarly, if a downstream caspase is inhibited then the cascade would also stop.

Furthermore, and as is described above, the speculation of the Examiner that inhibitory molecules are over-expressed in diseased cells may not be true. A skilled person would know that it is possible that these inhibitory molecules are actually underexpressed.

A skilled person would understand the teaching of Colussi *et al.* to show that a variety of factors could come into play in terms of the inhibition of caspases, and that inhibition is not even guaranteed to occur. Furthermore, the skilled person would also relate the teachings on inhibition to the other key teachings of Colussi *et al.* Namely, that to create an auto-activating molecule that is not inhibited, a fusion of procaspase 3 and a caspase 2 domain is preferred. It would be only reasonable for the skilled artisan to assume that the creation of a procaspase 3-caspase 2 fusion would be the instrumental factor in producing a

caspase that is not inhibited. Srinivasula *et al.* only teach the rearrangement of domains of caspase 3 in order to create an autoactivating caspase. In any event, a combination of these two references would **still** follow a gene therapy approach, in complete contrast to the present invention.

The Examiner has also asserted that it would be obvious to replace Ricin A with a caspase as described by Srinivasula *et al.* in the immunoconjugate of the '894 patent due to the teaching of Keppler-Hafkemeyer *et al.* teaching that Ricin A induces apoptosis.

The fact that Srinivasula *et al.* does not teach the claimed caspases is discussed above. Furthermore, Keppler-Hafkemeyer *et al.* provide experiments showing that *Pseudomonas* endotoxin (PE) induces apoptosis. On page 16394, right column, Ricin A is mentioned in passing as one of a number of toxins that cause both arrest of protein synthesis and are capable of inducing apoptosis. Furthermore, on 16941, left column final paragraph, it is made clear that target cells are killed by these two distinct mechanisms, *i.e.* inhibition of protein synthesis and apoptosis. In addition, it is shown that apoptosis plays only a minor role in induction of cell death by Ricin A-mediated cell death when compared to the extent of the role of protein synthesis inhibition. Therefore, it would not be obvious to replace the molecule with an important and major mechanism of cell death being inhibition of protein synthesis, with a molecule that expresses only a minor mechanism of cell death, namely, apoptosis.

For these reasons a skilled artisan would not be led to produce caspase immunoconjugates that require activation, let alone constiutively active caspase immunoconjugates. Reconsideration and withdrawal of the pending obviousness rejection is earnestly solicited.

In view of the remarks presented herein, it is respectfully submitted that the present application is in condition for final allowance and notice to such effect is requested. If the Examiner believes that additional issues need to be resolved before this application can be passed to issue, the undersigned invites the Examiner to contact him at the telephone number provided below.

Respectfully submitted,

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